

**PCT**WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C08L 89/00, 89/06, C09H 5/00, A61K 9/48</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 99/33924</b> <b>(43) International Publication Date:</b> 8 July 1999 (08.07.99)
<b>(21) International Application Number:</b> PCT/US98/23484 <b>(22) International Filing Date:</b> 4 November 1998 (04.11.98)  <b>(30) Priority Data:</b> 97/16574 26 December 1997 (26.12.97) FR  <b>(71) Applicant (for all designated States except US):</b> WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> SCOTT, Robert [GB/BE]; Konigin Elisabethplein 26, bus 4, B-9100 Sint Niklaas (BE). CADE, Dominique [FR/FR]; 11, rue des Américains, F-68000 Colmar (FR). HE, Xiongwei [CN/FR]; 20, rue Ed. Richard, F-68000 Colmar (FR).  <b>(74) Agents:</b> RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		<b>(81) Designated States:</b> AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> GELATINE COMPOSITIONS  <b>(57) Abstract</b>  The invention concerns Gelatine compositions containing an additional setting system for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard gelatine capsules wherein the gelatine used is of non-bovine and non-pig origin and preferably derived from fish, poultry or plant sources. Especially preferred are film compositions for hard gelatine capsules prepared from fish gelatine.		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## Gelatine compositions

The invention concerns gelatine compositions containing an additional setting system for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard gelatine capsules wherein the gelatine used is of non-bovine and non-pig origin and preferably derived from fish, poultry or plant sources. Especially preferred are film compositions for hard gelatine capsules prepared from fish gelatine.

A second embodiment of the invention is the use of the film composition for the manufacturing of hard gelatine capsules by conventional dip moulding processes.

The gelatine used for hard gelatine capsules is traditionally produced by extraction from collagen containing mammalian tissues, particularly such as pig skin and bovine bone. Gelatine from pig and bovine origin are preferably used for their gelling, film forming and surface-active properties. The manufacture of hard gelatine capsules by dip moulding process exploits fully its gelling and film forming abilities. Such capsules are manufactured by dipping mould pins into a hot solution of gelatine, removing the pins from the gelatine solution, allowing the gelatine solution attached on pins to set by cooling, drying and stripping the so-formed shells from the pins. The setting of the solution on the mould pins after dipping is the critical step to obtain a uniform thickness of the capsule shell.

Fish collagen is a further source of gelatine. However, it has long been known that gelatine derived from fish collagen lacks much of the gelling and setting ability of mammalian gelatines which limits the fish gelatine application. It is only applicable for products where a high viscosity of the solution without gel formation is desired, for example, in glue or food manufacturing. In the field of predosed pharmaceuticals, the fish gelatine can be used for micro-encapsulation (WO 9620612).

A. N. Fraga et al. describe in J. Polym. Mater. 5 (1988) 49-55 the mechanical properties from fish Gelatines as a brittle behaviour characteristic of a glassy material at normal temperatures. Such a brittleness is very undesired property for a gelatine capsule.

Norland Products Inc. describe in Research Disclosure 1987, 788 that water solutions of fish gelatine remain liquid down to 10°C, whereas water solutions of mammalian gelatine must be heated to temperatures over 30°C to remain liquid. This behaviour of fish gelatine will not allow the use in the conventional dip moulding process at conventional temperatures because of its too low gelling temperature.

B. Leuenberger describes in Food Hydrocolloids 1991, 353-361 viscosity and gelation properties of different mammalian and fish gelatines with the conclusion that fish gelatine may be useful in applications where high solution viscosity without gel formation is desired.

Surprisingly it has been found that fish gelatine can be used to produce gelatine compositions with conventional properties by adding a setting system to the aqueous fish gelatine solution.

5 The aim of the invention is therefore the provision of gelatine compositions for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard gelatine capsules wherein the  
10 gelatine used is of non-bovine and non-pig origin and preferably derived from fish, poultry or plant sources, and wherein a setting system is added to the aqueous gelatine solution. Especially preferred are gelatine compositions for hard gelatine capsules prepared from fish gelatine.

15 Surprisingly this is achieved by the addition of a setting system and this allows the use of a wide range of gelatines from other sources than pigs or cattle for gelatine products for human consumption avoiding ethical and cultural problems.

The addition of a setting system to gelatine solutions with  
20 normally insufficient gelling behaviour, enables the adaptation of specific and desired gelling properties, especially for the production of hard gelatine capsules. For the production of such capsules it is extremely important that the film forming gelatine solution remaining on the  
25 mould pins after dipping is prohibited from flowing down the pins. Otherwise the obtained film will not have the desired uniform thickness.

Consequently hard gelatine capsules from other than mammalian gelatine sources can be produced with the same equipment as for conventional hard gelatine capsules in the range of same process conditions. Furthermore capsules produced from  
5 compositions of the instant invention have the same dimensional specifications and allow the use of the existing filling machinery and do not require specific and new equipment for the capsule users. The capsules produced from the gelatine compositions of the invention have also  
10 acceptable mechanical and dissolution properties.

The gelatine concentration in the dipping solution is in a range of 10 to 60 %, preferably in the range of 20 to 40 % by weight.

The setting system consist of a hydrocolloid or mixtures of  
15 hydrocolloids and may contain in addition cations and / or sequestering agents.

Suitable hydrocolloids or mixtures producing synergistic properties may be selected from natural seaweeds, natural seed gums, natural plant exudates, natural fruit extracts,  
20 bio-synthetic gums, bio-synthetic processed starch or cellulosic materials, preferred are the polysaccharides.

The preferred polysaccharides are alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum,  
25 karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan, galactomannan, funoran, and other

exocellular polysaccharides. Preferred are exocellular polysaccharides.

The preferred exocellular polysaccharides are xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, dextran.

The preferred hydrocolloids are kappa-carrageenan or gellan gum or combinations like xanthan with locust bean gum or xanthan with konjac mannan.

10 Among the setting systems mentioned above, the systems of kappa-carrageenan with cation and gellan gum with cation are specifically preferred. They produce high gel strength at low concentrations and have excellent compatibility with gelatine.

15 The amount of the hydrocolloid is preferably in the range of 0.01 to 5 % by weight and especially preferred 0.03 to 1.0 % in the aqueous gelatine solution.

The cations are preferably selected from ,  $K^+$ ,  $Na^+$ ,  $Li^+$ ,  $NH_4^+$ ,  $Ca^{++}$  or  $Mg^{++}$ , for kappa-carrageenan are preferred  $K^+$ ,  $NH_4^+$  or  $Ca^{++}$ . The amount of cations is preferably lower than 3 %, especially 0.01 to 1 % by weight in the aqueous gelatine solution.

The preferred sequestering agents are ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid, tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta

cyclodextrin and combinations thereof. Especially preferred is ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof. The amount is preferably lower than 3 %, especially 0.01 to 1 % by weight of the dipping solution.

- 5 The gelatine capsules or films produced from the solutions as described will consequently contain by weight of 7 to 17 % of water, 83 to 93 % of gelatine, 0.01 to 10 %, preferably 0.05 to 5 % of hydrocolloids, less than 5 %, preferably 0.01 to 3 % of cations depending on the hydrocolloids used, and  
10 optionally less than 5 %, preferably 0.01 to 3 % of sequestering agents.

Capsules or films with the inventive gelatine compositions may be manufactured with conventional machines by the conventional processes like extrusion moulding, injection  
15 moulding, casting or dip moulding.

The inventive gelatine compositions may contain additionally acceptable plasticizers in an range from about 0 to 40 % based upon the weight of the gelatine. Suitable plasticizers are polyethylene glycol, glycerol, sorbitol, sucrose, corn  
20 syrup, fructose, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di- or triacetates of glycerol, natural gums or the like as well as mixtures thereof.

The inventive gelatine compositions may contain in a further  
25 aspect additionally pharmaceutically or food acceptable coloring agents in the range of from 0 to 10 % based upon the weight of the gelatine. The coloring agents may be selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or



indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes or mixtures thereof. Examples are patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C  
5 yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, brilliant black BN, carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract,  
10 clorophyllin, canthaxanthin, caramel, or betanin.

The shaped final product from gelatine compositions of the invention may be coated with a suitable coating agent like cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate,  
15 hydroxypropylmethyl cellulose phthalate, hydroxyalkyl methyl cellulose phthalates or mixtures thereof to provide e.g. enteric properties.

The gelatine compositions of the invention may be used for the production of containers for providing unit dosage forms  
20 for example for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, flavouring agents and the like.

The inventive gelatine compositions may be useful for the encapsulation of caplets in a capsule, especially in a tamper-proof form. The encapsulation of a caplet in a capsule  
25 is preferred processed by cold shrinking together capsule parts, which are filled with a caplet, which comprises the steps providing empty capsule parts, filling at least one of said capsule parts with one or more caplets, putting said

capsule parts together, and treating the combined capsule parts by cold shrinking.

The inventive gelatine compositions are also useful for encapsulating and sealing the two capsule halves in a process  
5 in which one or more layers of the composition are applied over the seam of the cap and body, or by a liquid fusion process wherein the filled capsules are wetted with a hydroalcoholic solution that penetrates into the space where the cap overlaps the body, and then dried.

10 A specific embodiment of the instant invention is a hard gelatine capsule from fish gelatine filled with fish oil.

The improved properties of the gelatine compositions are demonstrated by the following examples:

#### Example 1

15 To 3.39 kg of deionised water is added 5 g of potassium acetate (0.10% by weight in the solution), followed by addition of 10 g kappa-carrageenan (0.20% by weight) under stirring at about 70°C. When a clear solution is obtained 1.60 kg of fish gelatine (32% by weight) are added at 60°C  
20 under slow stirring until the gelatine is completely dissolved and the solution is defoamed.

The fish gelatine solution thus prepared is then poured into a dipping dish of a pilot machine of conventional hard gelatine capsule production equipment. While keeping the  
25 temperature of dipping fish gelatine solution at about 50°C, natural transparent hard fish gelatine capsules of size 1 were produced according to the conventional process with the

same dimensional specifications to the conventional hard gelatine capsules.

#### Example 2

To 5 kg of fish gelatine solution at 60°C, prepared according to example 1, are added 32.6 g of titanium dioxide previously dispersed into a small quantity of water. After homogenising the solution, it is poured into the dipping dish, and white opaque hard fish gelatine capsules of size 1 were produced as in the example 1.

10 The capsules from both examples have excellent dissolution properties as demonstrated in Fig. 1, showing the percentage of acetaminophen dissolved from capsules immersed in deionised water at 37°C (USP XXIII) as a function of dissolution time.

## Claims

1. Gelatine compositions consisting of a gelatine of non-bovine and non-pig origin and an additional setting system.
- 5 2. Gelatine compositions according to claim 1, wherein the gelatine is derived from fish, poultry or plants.
3. Gelatine compositions according to claim 1, wherein the gelatine is fish gelatine.
4. Gelatine compositions according to claim 1, wherein the  
10 setting system consists of hydrocolloids.
5. Gelatine compositions according to claim 1, wherein the setting system contains optionally cations and / or sequestering agents.
6. Gelatine compositions according to claim 1, wherein the  
15 gelatine is contained in an amount of 83 to 93 % by weight with a water content of 7 to 17 % by weight and the hydrocolloids are contained in an amount of 0.01 to 10 %, preferably 0.05 to 5 % by weight and cations in an amount of less than 5 %, preferably 0.01 to 3 % by  
20 weight.
7. Gelatine compositions according to claim 1, wherein the setting system contains optionally sequestering agents in an amount of less than 5 %, preferably 0.01 to 3 % by weight.

8. Gelatine compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from polysaccharides.
- 5 9. Gelatine compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from alginates, agar gum, guar gum, locust bean gum (carob), carrageenan, tara gum, gum arabic, ghatti gum, Khaya grandifolia gum, tragacanth gum, karaya gum, pectin, arabian (araban), xanthan, gellan, starch, Konjac mannan,  
10 galactomannan, or funoran.
10. Gelatine compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from exocellular polysaccharides.
- 15 11. Gelatine compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from xanthan, acetan, gellan, welan, rhamsan, furcelleran, succinoglycan, scleroglycan, schizophyllan, tamarind gum, curdlan, pullulan, or dextran.
- 20 12. Gelatine compositions according to claim 1, wherein the hydrocolloids of the setting system are selected from gellan gum or kappa-carrageenan.
- 25 13. Gelatine compositions according to claim 1, wherein the optional sequestering agent or mixture of sequestering agents of the setting system is selected from ethylenediaminetetraacetic acid, acetic acid, boric acid, citric acid, edetic acid, gluconic acid, lactic acid, phosphoric acid; tartaric acid or salts thereof, methaphosphates, dihydroxyethylglycine, lecithin or beta cyclodextrin.

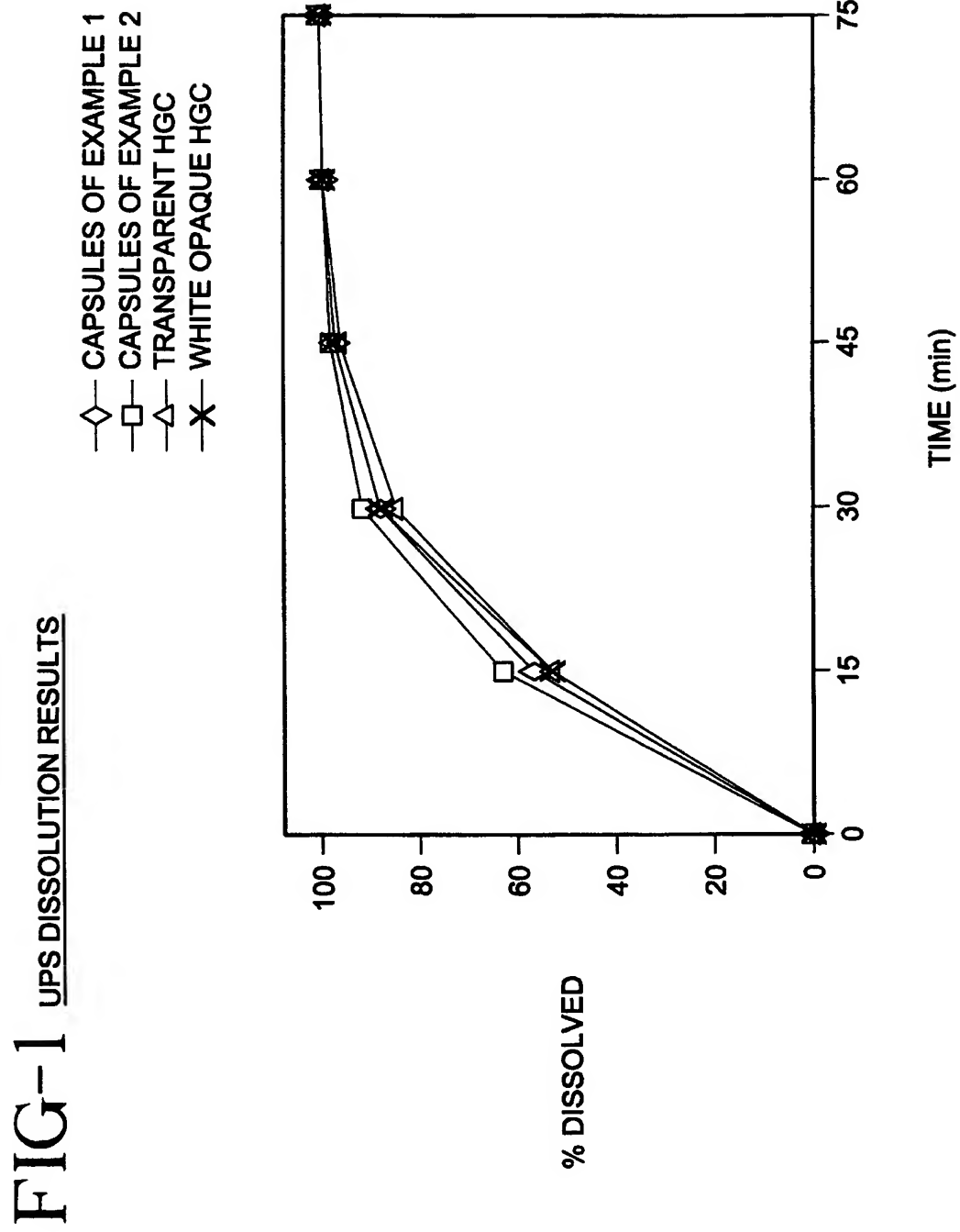
14. Gelatine compositions according to claim 13, wherein the sequestering agent or mixture of sequestering agents is selected from ethylenediaminetetraacetic acid or salts thereof or citric acid or salts thereof.
- 5 15. Gelatine compositions according to claims 1 to 14 containing additionally plasticizers in an range from about 0 to 40 % based upon the weight of the gelatine.
- 10 16. Gelatine composition according to claim 15 wherein the plasticizer or mixture of plasticizers is selected from polyethylene glycol, glycerol, sorbitol, sucrose, corn syrup, fructose, dioctyl-sodium sulfosuccinate, triethyl citrate, tributyl citrate, 1,2-propyleneglycol, mono-, di- or triacetates of glycerol, or natural gums.
- 15 17. Gelatine compositions according to claims 1 to 16 containing additionally coloring agents in an range from about 0 to 10 % based upon the weight of the cellulose ether.
- 20 18. Gelatine compositions according to claim 17 wherein the coloring agent or mixture of coloring agents is selected from azo-, quinophthalone-, triphenylmethane-, xanthene- or indigoid dyes, iron oxides or hydroxides, titanium dioxide or natural dyes.
- 25 19. Gelatine compositions according to claim 17 wherein the coloring agent or mixture of coloring agents is selected from patent blue V, acid brilliant green BS, red 2G, azorubine, ponceau 4R, amaranth, D+C red 33, D+C red 22, D+C red 26, D+C red 28, D+C yellow 10, yellow 2 G, FD+C yellow 5, FD+C yellow 6, FD+C red 3, FD+C red 40, FD+C blue 1, FD+C blue 2, FD+C green 3, or brilliant black BN.

20. Gelatine compositions according to claim 17 wherein the coloring agent or mixture of coloring agents is selected from carbon black, iron oxide black, iron oxide red, iron oxide yellow, titanium dioxide, riboflavin, carotenes, anthocyanines, turmeric, cochineal extract, chlorophyllin, canthaxanthin, caramel, or betanin.
21. Containers for unit dosage forms for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, or flavouring agents produced from the gelatine compositions according to claims 1 to 20.
22. Container according to claim 21 which is a pharmaceutical capsule.
23. Containers according to claims 21 or 22, characterized in that it has a coating.
24. Coated container according to claim 23 wherein the coating is selected from cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylic acid gelatines, hypromellose phthalate, hydroxypropylmethyl cellulose phthalate hydroxyalkyl methyl cellulose phthalates or mixtures thereof.
25. Caplets encapsulated in Gelatine compositions according to claims 1 to 20.
26. Capsules according to claim 21 or 22 characterized in that the capsule halves are sealed with one or more layers of the gelatine composition according to claims 1 to 20.
27. Capsules according to claim 21 or 22 characterized in that the capsule halves are sealed by a liquid fusion process.

28. Capsules according to claim 21 or 22 containing products derived from fish, preferred fish oil.
29. Aqueous solutions of gelatine compositions according to claims 1 to 20 for the manufacturing of gelatine capsules.
30. Aqueous solutions according to claim 29, containing gelatine in an amount of 10 to 60 %, preferably 20 to 40 % by weight, hydrocolloids in an amount of 0.01 to 5 %, preferably 0.03 to 1.0 % by weight and cations in an amount less than 3 %, preferably 0.01 to 1 % by weight of the aqueous solution.
31. Aqueous solutions according to claim 29 or 30, containing optionally sequestering agents in an amount of less than 3 %, preferably 0.01 to 1 % by weight of the aqueous solution.
32. Use of aqueous gelatine solutions according to claims 29 to 31 for the manufacturing of hard gelatine capsules in a dip moulding process.
33. Manufacturing of hard gelatine capsules from aqueous gelatine solutions according to claims 29 to 31 in a dip moulding process with conventional hard gelatine capsules process parameters and equipment.



1/1



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23484

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C08L89/00 C08L89/06 C09H5/00 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08L C09H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 20612 A (TASTEMAKER) 11 July 1996 cited in the application see page 5, line 9 - line 20 ---	1-4, 8, 9, 29
A	EP 0 284 569 A (LUISI PIER LUIGI PROF. DR.) 28 September 1988  see column 5, line 34 - column 6, line 35 ---	1, 4, 8, 9, 15, 16, 21, 22, 29, 32, 33
A	US 5 484 888 A (HOLZER) 16 January 1996  see abstract see column 1, line 10 - line 17 ---  -/--	1-3, 22, 29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

5 March 1999

Date of mailing of the international search report

15/03/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Mazet, J-F

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23484

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 345 885 A (MERCK & CO. INC.) 13 December 1989 see page 2, line 46 - line 47 see page 3, line 6 ---	1,4,5, 8-12
A	DATABASE WPI Week 8826 Derwent Publications Ltd., London, GB; AN 88-179849 XP002076465 & JP 63 117761 A (TSUJI S), 21 May 1988 see abstract -----	21-24,26

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23484

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9620612 A	11-07-1996	US 5603952 A AU 684683 B AU 4603796 A CA 2208793 A EP 0797394 A JP 10512141 T	18-02-1997 18-12-1997 24-07-1996 11-07-1996 01-10-1997 24-11-1998
EP 284569 A	28-09-1988	CH 674370 A AU 1421988 A WO 8807381 A JP 1503148 T US 5294249 A	31-05-1990 02-11-1988 06-10-1988 26-10-1989 15-03-1994
US 5484888 A	16-01-1996	NONE	
EP 345885 A	13-12-1989	US 4876105 A CA 1337391 A DE 68924371 D DE 68924371 T JP 2109950 A JP 2823241 B	24-10-1989 24-10-1995 02-11-1995 28-03-1996 23-04-1990 11-11-1998